

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Gravidity, parity, blood pressure, and mortality among women in Bangladesh from the HEALS cohort
<b>AUTHORS</b>	Shih, Yu-Hsuan; Scannell Bryan, Molly; Parvez, Faruque; Uesugi, Keriann; Shahriar, Mohammed; Ahmed, Alauddin; Islam, Tariqul; Ahsan, Habibul; Argos, Maria

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Tao Liu Guangdong Provincial Center for Disease Control and Prevention, China
<b>REVIEW RETURNED</b>	01-Mar-2020

<b>GENERAL COMMENTS</b>	<p>Thanks for giving me an opportunity to review this study. This study evaluated the association of parity and gravidity with blood pressure, hypertension, and all-cause mortality in Bangladeshi women who were recruited in a cohort study. They concluded that nulliparity and nulligravidity appear to be associated with higher blood pressure and subsequent elevated risks of mortality among women in rural Bangladesh. Generally, this is a well written manuscript. I have several concerns.</p> <ol style="list-style-type: none"><li>1. The authors need to give brief information of the cohort study in the abstract methods section. For example, when the cohort started, when the women were recruited, and when their blood pressure were measured.</li><li>2. Please give the citations in the Line 20-24 in Page 4.</li><li>3. The authors simply added 10 and 5 mmHg to the observed systolic and diastolic blood pressure of participants who had taken any an antihypertensive medication, which is arbitrary. I suggest the authors to exclude these participants in the analyses on their blood pressure, because there were only 2.4% of them.</li><li>4. How was the baseline and follow-up investigation conducted? Face to face interview or other ways?</li><li>5. The participants recruited were aged between 18-75 years, which leads to several questions. For example, those with older ages may cannot precisely recall history of pregnancy, which may lead to recall bias. These older participants may already have hypertension or higher blood pressure, which may be mainly related to aging or other factors. Therefore, I do not suggest the authors to include these older participants in their analyses.</li><li>6. As the authors stated in the introduction section, the higher blood pressure in nulliparous and nulligravid women may be due to their poor health status, such as polycystic ovary syndrome and uterine leiomyoma. However, the authors did not collect this information and adjust for them in the results, which should be mainly discussed in the limitation.</li></ol>
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	<p>7. why did not the authors show the other general demographic characteristics of participants in Table 1, such as occupation, home income?</p> <p>8. In Line 24-29 at Page 11, the authors stated that “After stratifying at 45 years of age, the associations were attenuated for women aged <math>\leq 45</math> years, while larger effect sizes were seen for women aged <math>&gt; 45</math>”. However, I found stronger association between parity 2+ and diastolic pressure in women less than 45 years. Similar results in Table 3.</p>
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<b>REVIEWER</b>	Mariam Kunjachen Maducolil Women's Wellness and Research Centre Doha Qatar
<b>REVIEW RETURNED</b>	18-Mar-2020

<b>GENERAL COMMENTS</b>	<p>This article is well composed .The subject and the findings are very relevant to women's health . The objectives have been met and the article is appropriately referenced. However the statistical analysis should be entrusted to a trained statistician. Could not find any mention of ethical approval for this study.</p> <p>Suggestions Need to mention regarding ethical approval Statistics to be reviewed by a statistician</p>
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<b>REVIEWER</b>	Jelena Šarac Institute for Anthropological Research, Zagreb, Croatia
<b>REVIEW RETURNED</b>	13-May-2020

<b>GENERAL COMMENTS</b>	<p>The manuscript is written in a clear manner and it presents data from a large cohort located in a non-European setting, which is a major strength of this study. However, I wonder why some other covariates were not included since the study is of longitudinal nature and participants are followed for a long time. For example, I think monthly income or similar should, together with education and land owning, be included in the discussion on the relationship between socioeconomic factors and blood pressure. Additionally, gestational weight gain could also be taken into account, since it is a factor that also influences blood pressure in pregnancy. The reference list is not very updated, there are a lot of references older than 10 years. This is something that should be revised.</p>
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## VERSION 1 – AUTHOR RESPONSE

### Reviewer #1

**1. The authors need to give brief information of the cohort study in the abstract methods section. For example, when the cohort started, when the women were recruited, and when their blood pressure was measured.**

**Response:** We have added the requested details to the methods section of the Abstract.

**2. Please give the citations in the Line 20-24 in Page 4.**

**Response:** We have added the requested citations.

**3. The authors simply added 10 and 5 mmHg to the observed systolic and diastolic blood**

**pressure of participants who had taken any an antihypertensive medication, which is arbitrary. I suggest the authors to exclude these participants in the analyses on their blood pressure, because there were only 2.4% of them.**

**Response:** As a sensitivity analysis, we excluded participants on antihypertension medications and presented the results in Supplemental Table 3. Results did not appreciably differ between the two analysis approaches, but we report both in the manuscript.

**4. How was the baseline and follow-up investigation conducted? Face to face interview or other ways?**

**Response:** We have added these details to the Methods section (i.e., Study population, Assessing mortality; Tracked-changes Manuscript Pages 4-7). Baseline and follow-up visits were all conducted face-to-face.

**5. The participants recruited were aged between 18-75 years, which leads to several questions. For example, those with older ages may cannot precisely recall history of pregnancy, which may lead to recall bias. These older participants may already have hypertension or higher blood pressure, which may be mainly related to aging or other factors. Therefore, I do not suggest the authors to include these older participants in their analyses.**

**Response:** We agree that recall bias is a potential limitation, particularly among older participants, and this has been described in the Discussion section of the manuscript (Tracked-changes Manuscript Page 17). A point of clarification, the eligibility criteria for the parent study was aged 18-75 years old; however, women included in our analyses were aged 18-65 years. This information has been added to the Results section for clarification (Tracked-changes Manuscript Page 9). Additionally, we include a citation to a recent publication by Espuet and Becker (2015), which suggests reliable and accurate assessment of parity and gravidity among Bangladeshi women over a 15 year period; therefore, we would like to present all results to readers, but noting the potential for some misclassification.

**6. As the authors stated in the introduction section, the higher blood pressure in nulliparous and nulligravid women may be due to their poor health status, such as polycystic ovary syndrome and uterine leiomyoma. However, the authors did not collect this information and adjust for them in the results, which should be mainly discussed in the limitation.**

**Response:** We have included a discussion of potential confounding by poor health status as a limitation of the study in the Discussion section (Tracked-changes Manuscript Page 17).

**7. why did not the authors show the other general demographic characteristics of participants in Table 1, such as occupation, home income?**

**Response:** Table 1 included the variables that were adjusted as covariates in the regression models. At the reviewer's request, we have additionally included occupation in Table 1. Income was not collected from study participants.

**8. In Line 24-29 at Page 11, the authors stated that "After stratifying at 45 years of age, the associations were attenuated for women aged  $\leq 45$  years, while larger effect sizes were seen for women aged  $> 45$ ". However, I found stronger association between parity 2+ and diastolic pressure in women less than 45 years. Similar results in Table 3.**

**Response:** We revised the sentence to read "the associations with nulliparity were attenuated". We have made edits accordingly in the manuscript (Tracked-changes Manuscript Page 11).

## **Reviewer #2**

### **1. Need to mention regarding ethical approval**

**Response:** A statement regarding ethical approval information is included in the Methods section "Study population" (Tracked-changes Manuscript Pages 5-6).

### **Reviewer #3**

**1. I think monthly income or similar should, together with education and land owning, be included in the discussion on the relationship between socioeconomic factors and blood pressure.**

**Response:** We have expanded our discussion of socioeconomic factors with blood pressure in the Discussion section (Tracked-changes Manuscript Page 17). Income was not collected from study participants, and this has been noted as a limitation of the present analyses.

**2. Gestational weight gain could also be taken into account, since it is a factor that also influences blood pressure in pregnancy.**

**Response:** We have included a discussion of gestational weight gain as a possible limitation in the Discussion section since it was not collected from study participants (Tracked-changes Manuscript Page 17). This is a consideration for the findings related to parous women, but the results observed for nulliparous women would not be impacted.

**3. The reference list is not very updated, there are a lot of references older than 10 years. This is something that should be revised.**

**Response:** We have updated references to include more recent publications to the manuscript.

### **VERSION 2 – REVIEW**

<b>REVIEWER</b>	Tao Liu Guangdong Provincial Center for Disease Control and Prevention, China
<b>REVIEW RETURNED</b>	01-Jun-2020

<b>GENERAL COMMENTS</b>	Thanks for giving me an opportunity to review the revised manuscript. Generally speaking, although all my questions were answered, most of them were answered roughly and some of them are still needed to be further answered.  1. The sensitivity analyses showed no substantial differences between results in participants with and without containing those who had taken any an antihypertensive medication. I suggest them just simply use the results excluding those who had taken any an antihypertensive medication as the main results. 2. Information of the baseline and follow-up investigation were still limited. The authors need to provide more detailed information. For example, where were the participants recruited, what is the sampling method and the sampling process, what is the response rate, etc.
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<b>REVIEWER</b>	Jelena Šarac Institute for Anthropological Research, Zagreb, Croatia
<b>REVIEW RETURNED</b>	09-Jun-2020

<b>GENERAL COMMENTS</b>	The authors have addressed all the comments adequately.
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### **VERSION 2 – AUTHOR RESPONSE**

Reviewer #1

1. The sensitivity analyses showed no substantial differences between results in participants with and without containing those who had taken any an antihypertensive medication. I suggest them just simply use the results excluding those who had taken any an antihypertensive medication as the main results.

Response: We apologize for the confusion around this issue with the original inclusion of the sensitivity analyses, which excluded the small percentage of participants on antihypertensive medications. Since the exclusion of participants on medications is recognized as a biased approach in the literature, we have decided to eliminate that analytical approach from the paper. While in our study, the effect estimates were not appreciably different between the main results and the sensitivity analyses due to the low prevalence of medication usage, we would like to present the main results based on an unbiased approach.

For reference, it is recognized that the observed blood pressure of participants on antihypertensive medication is lower than the underlying blood pressure had the person not been on antihypertensive medication, which would introduce a systematic negative bias if an appropriate adjustment for the effect of the medication is not applied. Excluding treated participants is one of the common approaches used by previous studies.<sup>1-6</sup> However, this approach selectively excludes participants with high underlying blood pressure and leads to shrinkage of effect estimates. It is suggested that this method is fundamentally flawed and should not be used.<sup>7</sup> The addition of a sensible constant to the observed blood pressure for participants taking medications is a widely accepted and unbiased approach to account for medication usage.<sup>8-10</sup> In our study, we elected to use this approach since it is considered to be a powerful adjustment method.<sup>7,11</sup>

2. Information of the baseline and follow-up investigation were still limited. The authors need to provide more detailed information. For example, where were the participants recruited, what is the sampling method and the sampling process, what is the response rate, etc.

Response: We have added additional information to the Methods section regarding the conduct of the baseline and follow-up visits (i.e., Study population; Tracked-changes Manuscript Pages 5-6).

Reference

1. Brand E, Wang JG, Herrmann SM, Staessen JA. An epidemiological study of blood pressure and metabolic phenotypes in relation to the G beta(3) C825T polymorphism. *J Hypertens*. 2003;21(4):729-737.
2. Iwai N, Baba S, Mannami T, et al. Association of sodium channel gamma-subunit promoter variant with blood pressure. *Hypertension*. 2001;38(1):86-89.
3. Matsubara M, Kikuya M, Ohkubo T, et al. Aldosterone synthase gene (CYP11B2) C-334T polymorphism, ambulatory blood pressure and nocturnal decline in blood pressure in the general Japanese population: the Ohasama Study. *J Hypertens*. 2001;19(12):2179-2184.
4. Schunkert H, Hense HW, Doring A, Riegger GAJ, Siffert W. Association between a polymorphism in the G protein beta 3 subunit gene and lower renin and elevated diastolic blood pressure levels. *Hypertension*. 1998;32(3):510-513.
5. Sethi A, Nordestgaard BG, Tybjaerg-Hansen A. Angiotensinogen gene polymorphism, plasma angiotensinogen, and risk of hypertension and ischemic heart disease: A meta-analysis. *Atherosclerosis Supplements*. 2003;4(2):41-41.
6. Rice T, Rankinen T, Province MA, et al. Genome-wide linkage analysis of systolic and diastolic blood pressure - The Quebec family study. *Circulation*. 2000;102(16):1956-1963.
7. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of

quantitative traits: antihypertensive therapy and systolic blood pressure. *Statistics in Medicine*. 2005;24(19):2911-2935.

8. Cui JS, Hopper JL, Harrap SB. Antihypertensive treatments obscure familial contributions to blood pressure variation. *Hypertension*. 2003;41(2):207-210.

9. Cui JS, Hopper JL, Harrap SB. Genes and family environment explain correlations between blood pressure and body mass index. *Hypertension*. 2002;40(1):7-12.

10. Neaton JD, Grimm RH, Prineas RJ, et al. Treatment of Mild Hypertension Study - Final Results. *Jama-J Am Med Assoc*. 1993;270(6):713-724.

11. Balakrishnan P, Beaty T, Young JH, Colantuoni E, Matsushita K. Methods to estimate underlying blood pressure: The Atherosclerosis Risk in Communities (ARIC) Study. *PLoS One*. 2017;12(7):e0179234.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Tao Liu Guangdong Provincial Center for Disease Control and Prevention, China
<b>REVIEW RETURNED</b>	26-Jun-2020
<b>GENERAL COMMENTS</b>	All my questions have been satisfactorily answered, and I suggest to accept it for publication.